

Conformational Properties of Molecules by *ab Initio* Quantum Mechanical Energy Minimization

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The recent literature on the determination of minimum energy conformations by *ab initio* quantum mechanical techniques is reviewed. The availability of computer-coded analytical first and second derivatives of the Hartree-Fock energy makes possible calculations that will be of significant assistance in structure determination of molecules. A short review of recent progress in empirical energy minimization and molecular dynamics is provided.

Introduction

The combined advances in computer technology and numerical analysis since the early 1950s are making possible the fulfillment of the long standing promise that quantum mechanics has held for biological areas of chemistry. Here we shall concentrate especially on a nonexhaustive review of representative recent studies that utilize *ab initio* quantum mechanical techniques to determine partially or fully energy minimized geometries in molecules.

General Considerations: Theory

The usual approach (1,2) for finding the energy for a molecular system is first to make the Born-Oppenheimer approximation, and second to assume the Hartree-Fock theory in which the simplest useful wave function, Ψ , for an n -electron system, is the single determinant of the occupied molecular orbitals $\{\psi\}$

$$\Psi = |\psi_1(1) \bar{\psi}_1(2) \psi_2(3) \dots \psi_m(n)| \quad (1)$$

The molecular orbitals are then taken as a truncated expansion of the basis functions $\{\phi\}$:

$$\psi_i = \sum C_{ri} \phi_r \quad (2)$$

The ϕ are normally in turn chosen to be expansions of Gaussian functions in which the expansion coefficients and Gaussian exponents are fitted to accurate calculations using Slater orbitals. Among the most widely used basis sets are the STO-3G and 4-31G basis sets (3,4)

developed by Pople and co-workers. The latter split valence set is of approximate double zeta quality. The expansion coefficients are then determined by solving the Roothaan equations and the energy is determined for a fixed nuclear configuration. Open shells require special modifications. The energy (for fixed nuclei) can be considerably improved by increasing the mathematical complexity of the molecular orbital expansion and/or by performing configuration interaction (CI) (5) or an equivalent procedure. One kind of CI wave function involves writing the total wave function as an expansion of determinants generated by placing the electrons in molecular orbitals unoccupied in the simplest description:

$$\Psi_{\text{Tot}} = \sum A_I \Psi_I \quad (3)$$

The coefficients A_I are then determined by the use of the variational principle and the electrostatic Hamiltonian and can thus be written as the solution of the matrix equation

$$\mathbf{H}\mathbf{A} = \mathbf{A}E \quad (4)$$

The self-consistent field (SCF) energy for the multi-configuration wave function can be written (6):

$$E = \sum_{i,j} \gamma_{r,s} \sum_{r,s} C_{ri} C_{sj} \langle r/h/s \rangle + \frac{1}{2} \sum_{ijkl} \Gamma_{ij,kl} \sum_{rstu} C_{ri} C_{sj} C_{tk} C_{ul} J_{rstu} + V_{nn} \quad (5)$$

where i,j,k,l are MO labels, r,s,t,u are AO labels. The one-electron Hamiltonian is h ; thus,

$$\langle r/h/s \rangle = \langle \phi_r/h/\phi_s \rangle \quad (6)$$

and the two-electron integrals are given by

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$$J_{rstu} = \langle \phi_r(1) \phi_s(1) / r_{12}^{-1} / \phi_t(2) \phi_u(2) \rangle \quad (7)$$

The coefficients γ_{ij} and $\Gamma_{ij,kl}$ are vector coupling coefficients defined by the solution A to the CI matrix. If we have only a single determinant of doubly occupied MO's, then

$$\begin{aligned} \gamma_{ii} &= 2 \\ \Gamma_{ii,jj} &= 4 \\ \Gamma_{ij,ji} &= -2 \end{aligned}$$

and all other coefficients vanish.

Great progress has been made in recent years toward finding and coding analytical expressions for the first and second derivatives of the general multiconfigurational energy; the most important initial contribution was made by P. Pulay (7). The energy gradient approach of Pulay provides a fast interaction algorithm by which the forces f_i on the atoms

$$f_i = -\partial E / \partial Q_i \quad (8)$$

are allowed to approach an equilibrium value by adjusting the nuclear positions until the net forces are zero. Pulay did not work out analytical second derivatives (which lead to force constants; this was first done by Pople et al. (8), who also found analytical first and second derivatives for the spin-orbital formulation of the Hartree-Fock energy as well as analytical first derivatives for second-order Moller-Plesset perturbation energy. Analytical energy first derivatives for the configuration interaction wave function were first provided by Kato and Morokuma (9), Goddard et al. (10,11) and Krishnan et al. (12). The Schaefer group (13) has very recently provided formulas for analytical second derivatives. In addition to the definitive review by Pulay (6), the interested reader may wish to consult Morokuma (14) and Schäfer (15) for recent updates.

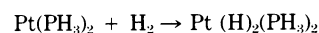
Calculations: Complete Optimization

The immediate goals of most quantum chemical studies are to be able to determine correct geometries and force constants for regions of a molecule's (or "supermolecule's") potential energy surface near local minima or saddle points (transition states). As always one ultimately wishes to examine systems of broad interest to all kinds of chemists. An example of the current state of affairs is given by Pulay et al. (16). In this paper a 4-21G basis set (17), similar in quality to a 3-21G basis (18), is used in combination with energy-gradient techniques and a few experimental vibrational frequencies to determine scaled force fields for glyoxal, acrolein, butadiene, formaldehyde and ethylene. Local valence internal coordinates (17) which minimize the coupling force constants are chosen. Qualitative infrared intensities are computed. Pulay et al. (16) conclude with an optimistic comment: "It now seems certain that, with the help of

information provided by the *ab initio* calculations, the force fields and normal vibrations of all reasonably simple organic molecules will be understood in the near future, after four decades of intensive experimental investigations."

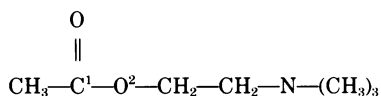
Documentation for this optimism is provided in a subsequent paper (19) with a completely theoretical prediction of the force field and vibrational spectra of pyridine. A number of *ab initio* gradient force-field calculations have now been performed mainly with the 4-21G basis: pyrimidine, pyridine, pyrazine and *s*-triazine (20); 1,4-cycloheptadiene, 1,3-cycloheptadiene and 1,3,5-cycloheptatriene (21); furan, pyrrole and thiophene (22), bicyclo (2.1.0)pentane (23), glycine (24), glycine methyl ester (25), 1,2-methylhydrazine (26), beryllocene (27), *N*-acetyl *N'*-methyl amides of glycine (28) and alanine (29), tricyclohexane, chair and boat; norbornane, quadricyclane, cubane, cyclopropane, cyclobutane and cyclohexane (30), acetylcholine (15), calicene (31), azxirene, oxinene, and thiirene (32), cyclobutadiene (33) (6-31G*), 1,3-dioxol-2-one, -thione and -onium and analogous 1,3-dithioles (34) (extended variable basis sets), the neutral and protonated DNA bases thymine, cytosine, adenine and guanine (35) (STO-3G optimization followed by single point 4-31G calculations), 1,2,4-triazole (36) (3-21G) and acetamide, fluoroacetamide, formamide oxine and 1,2-diformyl hydrazine (37) (3-21G), 2,3,4-hydroxypyridine (38) (3-21G). Schäfer (15) describes several cases in which energy-gradient calculations were essential in proper structure assignment: glycine (24) and methyl ester of glycine (25). Thus, energy-gradient calculations are proving to be an extremely useful tool when combined with complementary experimental studies; a recent structure determination for gaseous norbornane (39) utilized electron diffraction, microwave, Raman, infrared, and gradient calculations.

Energy-gradient calculations may be used to probe the transition-state regions of potential energy surfaces; the long-range implications to catalysis cannot be overestimated. Morokuma (14) has reviewed one way to proceed for reactions having heavy atoms. An effective core potential (ECP) model (40,41) which depends explicitly only on the valence electrons may be utilized. Such a model has been carefully tested by Obara et al. (42) and been shown to give good agreement for equilibrium and transition state geometries with all electron split valence *ab initio* calculations. Kitaura et al. (43) have examined the sample catalytic reaction of molecular hydrogen with two-coordinate platinum (0) and palladium (0) complexes:



by the ECP energy-gradient method using all single and double excitations. The geometry of a transition state, the activation barrier height and detailed mechanistic insight results from such calculations.

The potential importance of energy-gradient methods to structure-reactivity correlations is illustrated by the case of acetylcholine (15):



The C¹-O² bond distance is found to be considerably longer in AC than in methyl acetate (1.391 Å to 1.359 Å) with a corresponding reduction in the electron density (thus increased facility for nucleophilic attack) at C¹.

Calculations: Partial Optimization

A large number of calculations of biological interest have been performed that have used only partial geometry optimization due mostly to restrictions of computer time availability. We will review some of the most recent of these here. Cheney and Christoffersen (44,45) have utilized a molecular fragments *ab initio* method based on floating spherical Gaussian orbitals (FSGO) (46) to characterize the electronic structure and preferred conformation of a series of antiallergy agents. For oxamic acid derivatives, the biological activity *A* as represented by the dose to produce 50% of the anaphylactic response in a standard test (ED₅₀) is found to be correlated with the lowest unoccupied molecular orbital energy:

$$A = -\ln \text{ED}_{50} = -64.4\epsilon_a^* + 28.0$$

Thus charge transfer is implicated as a dominant receptor-drug interaction. For dioxamic acid derivative, however, potency is greatly enhanced and a further receptor-drug interaction involving the 3-NHCOCO₂H group is postulated. The same *ab initio* molecular fragment approach has also been used to develop a model for morphine and naloxone binding (47) at the opioid receptor and to develop a quantitative structure-activity relationship (QSAR) for the receptor binding and aryl hydrocarbon hydroxylase (AHH) induction for a series of dibenzo-*p*-dioxins and dibenzofurans (48,49). A hypothesis based on correlation of binding to cytosol protein with the second lowest unoccupied molecular orbital (4b_{1g} in TCDD) is that a charge-transfer mechanism contributes significantly to the receptor-toxin complex stability (48). The QSARs developed, however, show that receptor binding and AHH are affected differently by lateral substituent binding (49). The *ab initio* FSGO fragment model has been further approximated and reparameterized so as to be useful for very large systems by introducing pseudopotentials for the molecular fragments (50), and the method is tested with a calculation on formamide.

Base-stacking interactions in highly thermophilic bacteria have been studied by *ab initio* 4-31G calculations (51). The specific mutagenicity of O⁶ alkylated guanines is explained in an MINDO/3 (52) geometry optimized STO-3G study of hydrogen-bond base-pair interactions (53). STO-3G geometry optimization followed by 4-31G point calculations has been used to study preferred conformations in acetamide, *N*-methylformamide and *N*-methylacetamide (54). The possible disruptive role of F⁻

with RNA and DNA has been examined by a 4-31G geometry optimization for F⁻ uracil interaction (55). The preferred conformations of a number of polychlorinated biphenyls (PCBs) has been determined by STO-3G calculations (56) and a consequent binding model proposed to explain PCB and dioxin cytosol binding (57). The hexahalobenzenes (C₆F₆, C₆Cl₆, C₆Br₆, and C₆I₆) have been shown (58) to be planar in a double-zeta quality calculation (444 basis functions for C₆I₆).

Another Approach: Molecular Mechanics via Empirical Force Field

Predating *ab initio* energy minimization has been a large body of study called molecular mechanics which utilizes semiempirical force fields. Basically the idea is to define a potential energy function for the internal energy of a molecule that can be systematically parameterized to reproduce a certain spectroscopic, structural and/or thermodynamic data. An example of such an internal energy function which leads to a valence force field is (59)

$$\begin{aligned} E = & \sum \{ D_b [1 - e^{-\alpha(b-b_0)^2}]^2 - D_b \} + 1/2 \sum H_\theta (\theta - \theta_0)^2 \\ & + 1/2 \sum H_\phi (1 + s \cos n\phi) + 1/2 \sum H_X X^2 \\ & + \sum \sum F_{bb'} (b - b_0)(b' - b_0') \\ & + \sum \sum F_{\theta\theta'} (\theta - \theta_0)(\theta' - \theta_0') \\ & + \sum \sum F_{b\theta} (b - b_0)(\theta - \theta_0) \\ & + \sum \sum F_{\phi\theta\theta'} \cos \phi (\theta - \theta_0)(\theta' - \theta_0') \\ & + \sum \sum F_{XX'} XX' + \sum \epsilon [2(r^*/r)^9 \\ & - 3(r^*/r)^6] + \sum q_i q_j / r \end{aligned} \quad (9)$$

where the first term accounts for anharmonic bond stretches, the second term angle bends, the third term torsional energy variation, the fourth term allows for out-of-plane motion for planar fragments, terms five through nine are cross terms that account for coupling of different modes, and the last three terms account for nonbonded interactions. The subscript zero establishes an equilibrium or standard value. Algorithms based on steepest descent or Newton-Raphson methods are then used to find local energy minima and force constant estimates for subsequent computation of thermodynamic properties (60,61). The monograph by Burkert and Allinger (60) provides an excellent summary of the state of molecular mechanics into 1982. The computer programs MM1 (62,63) and MM2 (64) have been especially widely used for conformational studies on moderately sized molecules.

An important question relates to which is likely to provide the most accurate representation of nature, *ab initio* or molecular mechanics calculations. Considerations for a comparison on a test molecule are amount of computer time, level of basic set and/or degree of post-

SCF calculation, and how similar the test molecule is to the molecule set used to parameterize the force field for the molecular mechanics calculation. In one such test (39), a completely relaxed 4-21G calculation for norborane provided a significantly better model geometry for structure determination than did a molecular mechanics model (65).

Understanding protein structure and function through energy minimization and molecular dynamics (MD) constitutes an area of intense activity. Developments for energy minimization strategies of the Scheraga group at Cornell are summarized in a recent publication (66). The potential importance of array processor hardware to MD is emphasized by Berens and Wilson (67). The Karplus group at Harvard has recently announced the availability of a general macromolecular MD program CHARMM (68). Recent papers which give a preview of what is possible with molecular dynamics on proteins are provided by calculation of motion about the X-ray structure of bovine pancreatic trypsin inhibitor (69–71). A picture emerges from following atomic motion for 132 psec (71) that the atoms of the macromolecule vibrate about a conformation for a length of time and then “jump” over a finite energy barrier to a new conformational region. The excitement of this new area of computer chemistry is succinctly captured in the review by McCammon and Karplus (72).

Conclusion

There would appear to be reason for optimism that quantum mechanics is on the threshold of providing a framework for understanding the mechanistic details of biological chemistry. The application of systematic energy minimization techniques to *ab initio* calculations at the split valence basis level will likely become an important supplementary method for study of molecules of useful size.

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